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Abstract: Treatment of parapneumonic effusion in children remains controversial in the literature and in clinical practice. The aim of this study was to determine whether mutual consensus exists in the diagnosis and treatment of parapneumonic effusion in Central European countries. A questionnaire was sent to all directors of pediatric respiratory units in four adjacent Central European countries (Austria, France, Germany, Switzerland). The response rate was 61.8%. Responses reflected acceptable agreement regarding initial diagnostic procedures, as most centers performed chest X-ray and biological exams, followed by ultrasound, thoracocentesis, or computed tomography. However, antibiotic regimens were very heterogeneous, and the survey revealed complete lack of agreement on the indications and effusion volume threshold for invasive procedures, such as fibrinolytic instillation and thoracoscopy. In conclusion, apart from initial diagnostic procedures, this study showed a lack of mutual consensus among the four countries regarding the management of pediatric parapneumonic effusion. Multicenter prospective trials are clearly needed to acquire more evidence on the management of childhood parapneumonic effusion, enabling the development of evidence-based algorithms that could help to avoid unnecessary examinations with potential long-term side effects, such as radiation exposure at a young age. Pediatr Pulmonol. © 2015 Wiley Periodicals, Inc.

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Lack of Concordance in Parapneumonic Effusion Management in Children in Central Europe

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Summary. Treatment of parapneumonic effusion in children remains controversial in the literature and in clinical practice. The aim of this study was to determine whether mutual consensus exists in the diagnosis and treatment of parapneumonic effusion in Central European countries. A questionnaire was sent to all directors of pediatric respiratory units in four adjacent Central European countries (Austria, France, Germany, Switzerland). The response rate was 61.8%. Responses reflected acceptable agreement regarding initial diagnostic procedures, as most centers performed chest X-ray and biological exams, followed by ultrasound, thoracocentesis, or computed tomography. However, antibiotic regimens were very heterogeneous, and the survey revealed complete lack of agreement on the indications and effusion volume threshold for invasive procedures, such as fibrinolytic instillation and thoracoscopy. In conclusion, apart from initial diagnostic procedures, this study showed a lack of mutual consensus among the four countries regarding the management of pediatric parapneumonic effusion. Multicenter prospective trials are clearly needed to acquire more evidence on the management of childhood parapneumonic effusion, enabling the development of evidence-based algorithms that could help to avoid unnecessary examinations with potential long-term side effects, such as radiation exposure at a young age. Pediatr Pulmonol.

Key words: pleural effusion; pneumonia; empyema; child.

INTRODUCTION

Parapneumonic effusion (PE) is defined as any pleural effusion that is secondary to pneumonia—bacterial or viral—or lung abscess.[1] In children, PE is associated with high morbidity, but low mortality[2]; independent of the treatment modality, the long-term consequences for children are negligible, as the outcome in most cases is full recovery.[3]

Although the British Thoracic Society (BTS) published in 2005 national guidelines for the management of pleural infection in children,[4] the treatment of choice remains a matter of controversy in the literature and in clinical practice. While several studies have compared operative and non-operative approaches,[5–8] published evidence on the correct diagnosis and treatment of PE is scarce,[9] and clinical experience suggests the presence of heterogeneity between and within pediatric respiratory centers. Data on the extent of this heterogeneity are lacking. The diagnosis and treatment of PE have clinical and financial implications, as they may involve irradiation, antibacterial therapy, and invasive procedures. The development of evidence-based guidelines would be thus of interest for three main reasons.

Firstly, although radiation exposure is a concern in adults and children, the risk of radiation-related cancer development can be several times higher in children than in adults exposed to identical computed tomography (CT) examinations.[10] Given the likelihood that no low-dose radiation "threshold" for cancer induction exists, no amount of radiation should be considered to be absolutely

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Conflict of interest: None.

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safe.[11] Thus, evidence-based guidelines for the diagnosis and treatment of PE may reduce excessive exposure to radiation at a young age, as current diagnosis often involves lung CT and patients likely undergo repeated CT examination during the evolution of the disease.

Secondly, evidence-based consensus may allow adequate antibacterial therapy, reducing the risk of resistance development and overtreatment leading to side effects.

Lastly, guidelines may help to avoid unnecessary invasive procedures in children, which may lead to a reduction in morbidity, healthcare utilization, and associated costs.

The aim of this study was to determine whether mutual consensus has been reached on the diagnosis and treatment of PE in various pediatric pulmonology centers in adjacent countries. The hypothesis was that such mutual consensus exists, on the basis of knowledge transfer due to the exchange of trainees among centers. Participation of physicians and trainees in the field of pediatric pulmonology in small national and international scientific meetings is language dependent and organized by the French Association de Pneumo-Pédiatrie Inter-Régionale or the German Gesellschaft für Pädiatrische Pneumologie e.V. This survey addressed the clinical management of children with PE in hospitals in four Central European countries with French or German as the national language.

METHODS

Study Design and Sample

We conducted a questionnaire-based survey on the diagnosis and treatment of PE in Austria, France, Germany, and Switzerland. The questionnaire was sent by mail between July and December 2010 to all directors of pediatric respiratory centers, based on official country lists of these centers. Reminders were sent to directors who did not respond within 6 weeks.

In February 2015, a short Follow up survey was sent to all centers that had participated in the original study. This survey assessed specifically centers' adherence to BTS guidelines[3] for the management of pleural infection in children.

Questionnaires

A 16-item English-language questionnaire was developed for the main survey (Supplement 1). The questionnaire took about 15 minutes to complete. It was composed of general (e.g., number of patients per year), diagnostic (e.g., initial radiological examination used), and treatment (e.g., choice of antibiotics) sections, with a final item assessing respondents' interest in participating in a prospective multicenter study. Items had a structured response format; most questions were closed, with one possible answer, but some questions were multiple choice or offered the option of free-text answers (e.g., duration of antibiotic therapy, volume of pleural effusion).

In the 2015 Follow up survey the items were "No changes" or "Yes, we have changed our management of children with PE since 2010." In case of "Yes," the participants were asked whether the change was to follow the BTS guidelines or not.

Statistical Analysis

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Descriptive statistics were calculated. As not every center responded to every item and some centers reported multiple diagnosis and/or treatment methods, not all results add up to 100%.

RESULTS

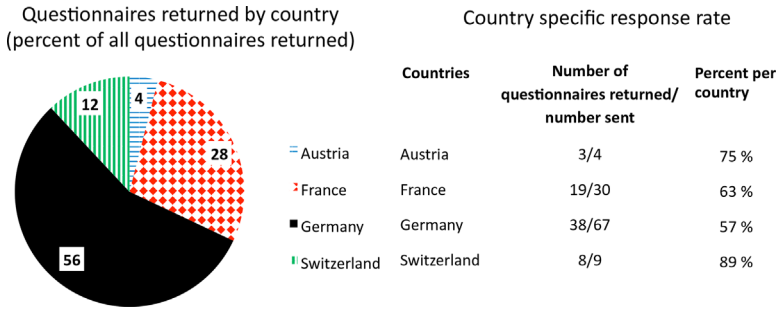
Of the 110 pediatric pulmonology centers contacted, 68 centers returned the 2010 questionnaire (61.80% response rate). The response rate varied among countries (Fig. 1). A median of 10 (min. 2, max. 40) cases of PE were treated annually per center. In 2010, 35 of 65 (53.85%) centers reported following the BTS guidelines[3] for the management of PE in children.

In 2015, 67 of the 68 centers that had participated in 2010 were re-contacted. The response rate to the 2015 survey was 74.62% (50 centers). Country-specific response rates were 66.66% (2/3) for Austria, 68.42% (13/19) for France, 68.42% (26/38) for Germany, and 100% (8/8) for Switzerland. As one center closed after returning the survey, data from 49 centers were analyzed. Thirty-two centers reported that they had not changed their management of PE since 2010. In 2015, seven additional centers reported following the BTS guidelines, bringing the total to 64.61% (42/65). Other centers reported changes in management involving the introduction of new standard operating procedures (three centers) or individual changes, such as the choice of antibiotics (seven centers).

Diagnostic Procedures

Upon clinical suspicion of PE, all centers reported performing the following radiological examinations: chest X-ray [CXR; 67/68 (98.5%)], ultrasound [US; 55/68 (80.88%)], ultrasound-guided thoracocentesis or drain placement [36/68 (52.94%)], and CT [17/68 (25%)]. After initial radiological examination, 18/67 (26.87%) centers reported the initiation of antibiotic therapy with no further imaging study.

In -three (4.41%) centers, antibiotic therapy was initiated with no initial laboratory examination and PE evolution was monitored. However, the majority [60/68 (88.24%)] of centers reported performing serum



Country specific response rate

Countries	Number of questionnaires returned/ number sent	Percent per country
Austria	3/4	75 %
France	19/30	63 %
Germany	38/67	57 %
Switzerland	8/9	89 %

Fig. 1. Response rate.

biochemistry and differential blood cell counts. Half the centers performed sputum culture and 44/68 (64.71%) centers reported performing thoracocentesis. All of these centers performed Gram staining/culturing of the pleural fluid obtained by thoracocentesis, 42/44 (95.45%) centers performed differential cell counts, and 39/44 (88.64%) centers performed biochemical analyses.

If not performed initially, thoracocentesis was performed based on the sole criterion of the clinical picture or severity of the illness in 21/66 (31.8%) centers. The other centers [45/66 (68.2%)] additionally assessed the size of the pleural effusion by CXR, US, and/or CT. The estimated size or volume of the pleural effusion was also used as a criterion for thoracocentesis performance, but this practice varied among centers (Fig. 2). Only 2/66 (3%) centers reported performing thoracocentesis for diagnostic purposes alone. The other centers used the procedure for fluid evacuation and/or in conjunction with drainage. Thoracocentesis was performed by pediatric surgeons [10/66 (15.1%)], pediatricians [10/66 (15.1%)], pediatric pulmonologists [10/66 (15.1%)], intensivists/anesthetists [8/66 (12.1%)], and thoracic surgeons [1/66 (1.5%)]. In 27/66 (40.9%) centers, various combinations of physicians from multiple disciplines were involved. Three (4.41%) centers reported performing diagnostic bronchoscopy.

Treatment

All (67/67) centers initiated antibiotic therapy intravenously. However, the choice, combination, and duration of intravenous antibiotic therapy varied among centers (Fig. 3). Twenty-four centers prescribed oral antibiotics initially. As for intravenous antibiotics, the choice, dosage, and duration of oral antibiotic treatment varied widely (Fig. 4).

Centers reported the consideration of chest drain insertion in the following cases: significant volume shown on radiological examinations [50/67 (74.6%)], increased effusion under conservative treatment [46/67 (68%)], and/or compromised respiratory function [60/67 (89.6%)]. In free-text responses, directors from three centers reported chest drain insertion in cases of persistent fever, thick fluid, and empyema, respectively. The criteria for this invasive procedure varied among centers. Eight of 63 (12.7%) centers reported the use of repeated thoracocentesis instead of chest drain insertion.

Centers used small-bore percutaneous drains [18/67 (26.9%)], pig-tail catheters [17/67 (25.4%)], and large-bore surgical drains [21/67 (31.3%)] for chest drainage. Eleven centers reported the use of more than one of these drain types. Similar to thoracocentesis, chest drain insertion was performed by pediatric/thoracic surgeons [24/68 (35.3%)], pediatricians [7/68 (10.3%)], pediatric pulmonologists [8/68 (11.8%)], intensivists/anesthetists [6/68 (8.8%)], and pediatric intensivists [1/68 (1.5%)]. Twenty-two of 68 (32.3%) centers reported the involvement of various physicians from multiple disciplines.

Thorascopy was performed based on the sole criterion of organized effusion/empyema or unfavorable clinical evolution in 18/57 (31.6%) and 12/57 (21.1%) centers, respectively. The remaining centers [27/57 (47.37%)] reported using a combination of effusion volume estimated by CXR, US, and/or CT; clinical picture; unfavorable clinical evolution after three to 30 days; and/or the presence of organized effusion/empyema. Use of the estimated size or volume of the pleural effusion as a criterion for thoracoscopy performance varied among centers.

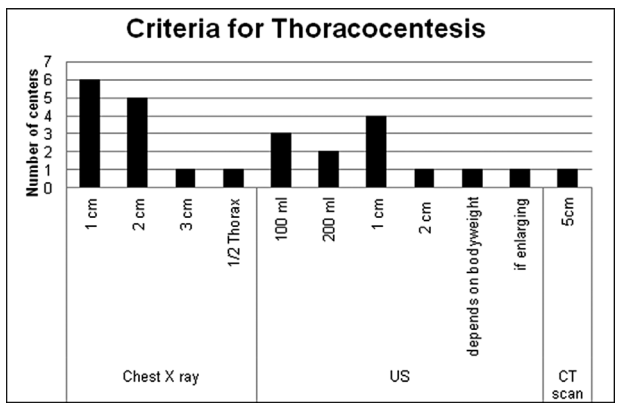
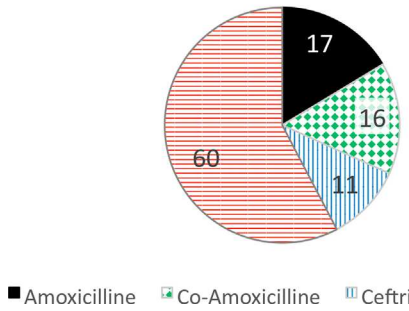


Fig. 2. Estimated size or volume of the pleural effusion as a criterion to perform a thoracocentesis.



	Dosage (mg/kg)		
	Minimum	Median	Maximum
Amoxicilline	80	100	200
Co-Amoxicilline	50	100	150
Ceftriaxone	50	100	150
	Duration (days)		
	Minimum	Median	Maximum
Amoxicilline	2	10	15
Co-Amoxicilline	7	10	15
Ceftriaxone	2	10	15

Fig. 3. Intravenous antibiotics as single prescription or in combination between two or three antibiotics. Sixty seven centres given intravenous antibiotics. The number of centres who give a specific intravenous antibiotics is shown. As many centres given then more than one intravenous antibiotic the total is >100%. Other: Flucloxacillin, Oxacillin, Piperacillin, Tazobactum, Cefuroxim, Cefotaxim, Cefotiam, Amikacin, Erythromycin, Meropenem, Rifampicin, Clindamycin.

Fibrinolytics were not used in 29/67 (43%) centers, always used in 7/67 (10%) centers, and used in certain cases in 31/67 (46%) centers. Urokinase was used in 33/38 (87%) centers and streptokinase was used in 2/38 (5%) centers. Dosages varied widely (Fig. 5) and the durations ranged from one to five days, with 75% of centers using 3-day regimens.

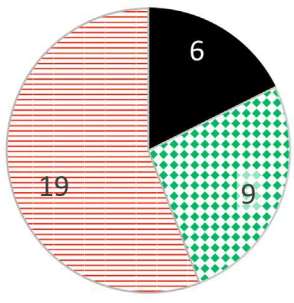
Almost all (84.6%) centers indicated that they would be interested in participating in a prospective, randomized multicenter study of the management of PE in children.

DISCUSSION

With this questionnaire-based survey, we demonstrated the lack of mutual consensus on the management of PE in children in Central European countries. We found variable diagnostic algorithms, very heterogeneous antibiotic regimens, and a lack of agreement with regard to the definitions of thresholds (e.g., effusion volume) and the use of invasive procedures (e.g., fibrinolytic instillation, thoracoscopy). This chaotic situation may have supported the interest of 85% of centers in participating in a prospective, randomized multicenter study of PE management in children.

To increase the chance of identifying mutual consensus due to the exchange of trainees and knowledge, the survey was conducted in four adjacent European countries: Austria, France, Germany, and Switzerland. We found consensus on the initial diagnostic approach, as most centers performed CXR with biological examinations (differential cell count, biochemistry), followed by US, thoracocentesis, and CT, if necessary. An evidence-based diagnostic algorithm would likely help to avoid unnecessary examinations, particularly those associated with potential long-term side effects, such as radiation exposure at a young age.

The choice, dosage, and duration of intravenous and oral antibiotics varied widely among centers. Empirical



	Dosage (mg/kg)		
	Minimum	Median	Maximum
Amoxicilline	50	90	120
Co-Amoxicilline	50	90	100
	Duration (days)		
	Minimum	Median	Maximum
Amoxicilline	7	14	28
Co-Amoxicilline	7	10	15

Fig. 4. Oral antibiotics as single prescription or in combination between two or three antibiotics. Twenty four centres given oral antibiotics. The number of centres who give a specific intravenous antibiotics is shown. As many centres given then more than one intravenous antibiotic the total is >100%. Other: Cefuroxim, Cefaclor, Clarythromycin, Erythromycin, Actromycin, Ravamycin, Pristinamycin, Rifampicin, Clindamycin.

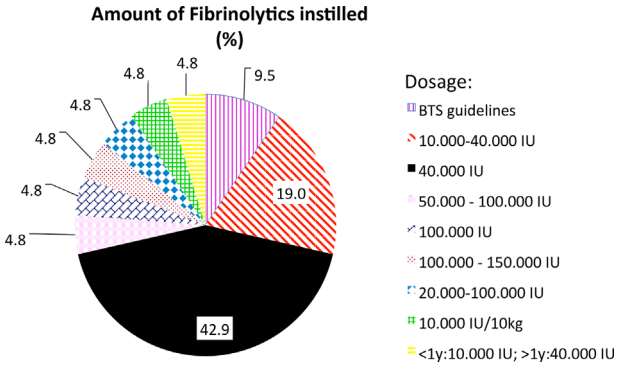


Fig. 5. Dosage of Fibrinolytics instilled.

treatment of community-acquired pneumonia must be active against pneumococcal infection, and should involve consideration of the local prevalence of antibiotic resistance, which varies regionally in.[12,13] A 2012 European Union survey revealed that 1% to <5% of invasive isolates of *Streptococcus pneumoniae* in Germany and Austria, but 10% to <25% of isolates in France, were not susceptible to penicillin or macrolides (2013). In 2013, the overall prevalence of penicillin resistance in Switzerland was about 15%, but this prevalence was about 20% in the western (French-speaking) part of the country.[14] Thus, the establishment of recommendations for antibiotic management across Europe may be difficult. Moreover, the administration of pneumococcal conjugate vaccine (PCV) to infants may have contributed to the significant decrease in antibiotic resistance levels in 2011, by eliminating infections and children's carriage of frequent classic resistant serotypes (2013).[15] Future studies must take this factor into consideration.

The indications for thoracoscopy and fibrinolytic instillation were also very heterogeneous among centers. The responses showed strong consensus, however, on the choice of urokinase over streptokinase. This preference makes sense, as urokinase has fewer side effects.[16] Streptokinase is associated with side effects such as fever (although this effect is reversible with discontinuation of administration),[17] and a higher risk of allergic reaction.[18] No center participating in our survey reported use of the new fibrinolytic intrapleural tissue plasminogen activator, but this product is emerging as a therapeutic option for children.[19,20]

The literature shows a lack of consensus on the best diagnostic and treatment methods for complicated pneumonia. In addition, meta-analysis is hampered by different interpretations of "conservative" or "non-operative" treatment, given the lack of clear definitions. For example, Avansino et al.[5] defined "primary non-operative therapy" as "children being treated initially with antibiotics and thoracocentesis and/or tube thoracotomy," although most physicians would consider thoracocentesis and thoracotomy to be operative interventions. In a large retrospective analysis of an administrative database, Goldin et al.[3] recently showed that half of more than 14,000 children hospitalized with effusion/empyema between 2003 and 2008 required only intravenous antibiotic therapy, raising the question of the degree of invasiveness required. In a systematic analysis of randomized controlled trials involving fibrinolytic use, Krenke et al.[9] found only minor evidence for the superiority of fibrinolytics over normal saline, or for the greater effectiveness of fibrinolytics compared with thoracoscopy.

Treatment of children with PE is associated with significant utilization of healthcare resources. Because healthcare systems differ throughout Europe, examination choices can be influenced by expense, rather than evidence.

Few studies have compared the costs of invasive and non-invasive management. In 2006, Sonnappa et al.[8] found that treatment with intrapleural urokinase was more economic than video-assisted thoracoscopic surgery (VATS). Two years later, Cohen et al.[21] postulated that the use of intrapleural fibrinolytic agents in pediatric patients reduced the costs associated with the treatment of empyema. The most recent publication, however, showed no overall cost difference between VATS and primary chest tube placement.[22]

As the outcome of PE is almost always favorable, independent of treatment, one might argue that the paucity of evidence for the optimal diagnosis and management is unimportant. However, the diagnosis and treatment of PE involve irradiation, antibacterial therapy, and invasive procedures with clinical and financial implications. Regrettably, our data do not allow the development of a flow chart or specific recommendations; however, a more ubiquitous approach to the management of PE could be obtained by the following means. First, an update of the 10-year-old BTS guidelines could be attempted, involving centers that do and do not follow the guidelines currently. Second, appropriate multicenter studies might produce evidence to define thresholds, such as effusion volume, to standardize procedures, mainly to avoid unnecessary interventions and the spread of antibiotic resistance. Finally, the establishment of a pan-European network guided by the European Respiratory Society (ERS) could be considered. Such a consortium would need to consider regional and national characteristics (e.g. antibiotic resistance), and include representatives from national pediatric pulmonology societies to increase adherence to the resulting recommendations.

Surprisingly, we discovered that three centers in our sample performed diagnostic bronchoscopy in cases of PE. The BTS guidelines do not recommend the routine use of this procedure. In addition, some pediatric

pulmonology centers reported that they encountered as few as two patients with PE per year. Given the likelihood that children with PE are treated in general pediatric settings as well as pediatric pulmonology centers, clinical evidence and associated guidelines would reduce patient burden. The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) has led to a significant reduction in the incidence of invasive pneumococcal diseases, such as pneumonia, septicemia, and meningitis.[23–25] However, PCV7 does not include the serotypes most commonly responsible for PE. An increase in the incidence of PE[26,2] prompted the development of a 13-valent PCV.[27] With its recent introduction in clinical practice, the epidemiology of empyema in children is changing again, as it did after the introduction of its precursor; the prevalence of PE is declining,[28] at least at present.

Limitations

As this survey was performed in central Europe, the findings may not be universally valid for all European countries. We did not include Great Britain in the survey, as the study was not designed to investigate compliance with its country-specific BTS guidelines. The questionnaire was sent only to hospitals with pediatric pulmonology units, which is a clear study limitation. However, we selected this approach because we expected less heterogeneity in pediatric pulmonology units and we aimed to assess interest in participation in a large randomized study.

Moreover, this study was limited by the potential risk for language translation error using an English questionnaire, and alternative interpretation of survey items. For example, items pertaining to the timing of investigation and multiple-choice questions may have been misinterpreted.

One might also argue that a response rate of 61.80% is not sufficient. However, although agreement is lacking on a minimal acceptable response rate, general consensus holds that at least half of the sample should have completed the survey instrument.[29]

With regard to irradiation, the questionnaire did not elicit exact details about dosage protocols for CXR or CT. The utilization of ultra-low-dose CT protocols should certainly be examined in any future prospective study, as exposure to radiation is of concern, particularly in children.

Finally, the survey was conducted in 2010, and does not necessarily reflect the management of PE in 2015. For that reason, we performed a Follow up study involving centers that participated in 2010. Only seven additional centers reported that they followed the BTS guidelines in 2015. Therefore, the management of PE remains heterogeneous.

CONCLUSION

In conclusion, this study revealed a lack of mutual consensus on the management of PE in children in four adjacent countries. The management of this disease remains center dependent. Due to the small number of patients treated in each center, only multicenter prospective studies can provide better evidence regarding the appropriate treatment of PE. In any future prospective study, clear definition of treatment modalities (non-operative versus operative) and qualitative and quantitative establishment of outcome indicators, such as pain and respiratory distress, would be important. As we have shown substantial heterogeneity in the management of PE in children, we clearly see the need for the establishment of an ERS or ERS/ATS (American Thoracic Society) task force to tackle the subject.

REFERENCES

1. Hamm H, Light RW. Parapneumonic effusion and empyema. Eur Respir J 1997;10:1150–1156.
2. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. Pediatrics 2010;125:26–33.
3. Goldin AB, Parimi C, Lariviere C, Garrison MM, Larison CL, Sawin RS. Outcomes associated with type of intervention and timing in complex pediatric empyema. Am J Surg 2012;203: 665–673.
4. Balfour-Lynn IM, Abrahamson E, Cohen G, Hartley J, King S, Parikh D, Spencer D, Thomson AH, Urquhart D. BTS guidelines for the management of pleural infection in children. Thorax 2005;60:1–21.
5. Avansino JR, Goldman B, Sawin RS, Flum DR. Primary operative versus nonoperative therapy for pediatric empyema: a meta-analysis. Pediatrics 2005;115:1652–1659.
6. Kurt BA, Winterhalter KM, Connors RH, Betz BW, Winters JW. Therapy of parapneumonic effusions in children: video-assisted thoracoscopic surgery versus conventional thoracostomy drainage. Pediatrics 2006;118:e547–e553.
7. Epaud R, Aubertin G, Larroquet M, Pointe HD, Helardot P, Clement A, Fauroux B. Conservative use of chest-tube insertion in children with pleural effusion. Pediatr Surg Int 2006;22:357–362.
8. Sonnappa S, Cohen G, Owens CM, van Doorn C, Cairns J, Stanojevic S, Elliott MJ, Jaffe A. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. Am J Respir Crit Care Med 2006;174:221–227.
9. Krenke K, Peradzynska J, Lange J, Ruszczynski M, Kulus M, Szajewska H. Local treatment of empyema in children: a systematic review of randomized controlled trials. Acta Paediatr 2010;99:1449–1453.
10. Radiology SfP. Radiation Risks and Pediatric Computed Tomography (CT): A Guide for Health Care Providers 2012 [Internet]. National Cancer Institut at the National Institutes of Health. Available from: http://www.cancer.gov/cancertopics/causes/radiation/radiation-risks-pediatric-CT.
11. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013;346:f2360.
12. European Centre for Disease Prevention and Control. 2013. Antimicrobial resistance surveillance in Europe 2012. Annual

Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC.
13. Lynch JP, Zhanel 3rd. Streptococcus pneumoniae: does antimicrobial resistance matter? Semin Respir Crit Care Med 2009;30: 210–238.
14. Hauser C, Kronenberg A, Mühlemann K. Trends of antimicrobial-resistance in Streptococcus pneumoniae in Switzerland 2004–2011: active surveillance versus use of routine microbiology data. 23rd European Congress of Clinical Microbiology and Infectious Diseases. Berlin, Germany: European Society of Clinical Microbiology and Infectious Diseases; 2013.
15. Kempf M, Varon E, Lepoutre A, Gravet A, Baraduc R, Brun M, Chardon H, Cremniter J, Croize J, Dalmay F, et al. Decline in antibiotic resistance and changes in the serotype distribution of Streptococcus pneumoniae isolates from children with acute otitis media; a 2001–2011 survey by the French Pneumococcal Network. Clin Microbiol Infect 2015;21:35–42.
16. Bouros D, Schiza S, Siafakas N. Utility of fibrinolytic agents for draining intrapleural infections. Semin Respir Infect 1999;14: 39–47.
17. Barletta JF. Streptokinase and urokinase for the treatment of pleural effusions and empyemas. Ann Pharmacother 1999;33: 495–498.
18. Bouros D, Schiza S, Patsourakis G, Chalkiadakis G, Panagou P, Siafakas NM. Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: A prospective, double-blind study. Am J Respir Crit Care Med 1997;155: 291–295.
19. Ray TL, Berkenbosch JW, Russo P, Tobias JD. Tissue plasminogen activator as an adjuvant therapy for pleural empyema in pediatric patients. J Intensive Care Med 2004;19:44–50.
20. Hanson SJ, Havens PL, Simpson PM, Nugent ML, Wells RG. Intrapleural alteplase decreases parapneumonic effusion volume in children more than saline irrigation. Pediatr Pulmonol 2015. (Epub adhead of print).
21. Shah SS, Ten Have TR, Metlay JP. Costs of treating children with complicated pneumonia: a comparison of primary video-assisted thoracoscopic surgery and chest tube placement. Pediatr Pulmonol 2010;45:71–77.
22. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003; 348:1737–1746.
23. Kaplan SL, Mason EO, Jr., Wald ER, Schutze GE, Bradley JS, Tan TQ, Hoffman JA, Givner LB, Yogev R, Barson WJ. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. Pediatrics 2004;113:443–449.
24. Poehling KA, Talbot TR, Griffin MR, Craig AS, Whitney CG, Zell E, Lexau CA, Thomas AR, Harrison LH, Reingold AL, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA 2006; 295:1668–1674.
25. Grijalva CG, Nuorti JP, Zhu Y, Griffin MR. Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. Clin Infect Dis 2010;50:805–813.
26. Strachan RE, Cornelius A, Gilbert GL, Gulliver T, Martin A, McDonald T, Nixon GM, Roseby R, Ranganathan S, Selvadurai H, et al. Bacterial causes of empyema in children, Australia, 2007-2009. Emerg Infect Dis 2011;17:1839–1845.
27. Grijalva CG, Pelton SI. A second-generation pneumococcal conjugate vaccine for prevention of pneumococcal diseases in children. Curr Opin Pediatr 2011;23:98–104.
28. Moore CE, Paul J, Foster D, Mahar SA, Griffiths D, Knox K, Peto TE, Walker AS, Crook DW, Oxford Invasive Pneumococcal Surveillance G. Reduction of invasive pneumococcal disease 3 years after the introduction of the 13-valent conjugate vaccine in the oxfordshire region of England. J Infect Dis 2014;210: 1001–1011.
29. Draugalis JR, Coons SJ, Plaza CM. Best practices for survey research reports: a synopsis for authors and reviewers. Am J Pharm Educ 2008;72:11.

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